THE USE OF CONVALESCENT SCARLET FEVER AND MEASLES SERA IN PROPHYLAXIS AND THERAPY*

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IT is well known that an attack of certain infectious diseases confers lasting, even lifelong immunity on the recovered individual. These individuals, known as immunes, can have intimate contact with these infectious diseases and still not contract them. This resistance results because the disease has caused the active and continuous development of immune substances in the tissues or blood, or both, of the recovered individuals. These substances neutralize the infectious agent when it attempts to gain entrance into the body, and, thereby, prevent infection.

This natural method of the development of immunity has been utilized in some diseases for the preparation, in animals, of serums for preventing or treating specific, infectious diseases. Diphtheria antitoxin is an example of one of these serums prepared by inoculating horses with the diphtheria toxin, which stimulates the development of antitoxin, just as the clinical disease diphtheria causes this effect in patients who recover. Diphtheria antitoxin, when injected under the skin of a child exposed to this disease is almost 100 per cent efficient in preventing the development of diphtheria. In this way diphtheria antitoxin developed actively in the horse is transferred passively to the exposed child. The resulting passive immunity is a temporary one which lasts for two to three weeks. Although of a temporary nature it is extremely important immediately to protect susceptible children from diphtheria, especially young children in whom the mortality is high. Diphtheria antitoxin, of course, also is very efficient therapeutically.

Weisbecker[1] in 1897 was the first one to find out that human serum obtained from an individual recently recovered from scarlet fever, when injected into another will cause a passive immunity, and also, will give excellent results with rapid cure in the treatment of patients in whom scarlet fever has already developed.

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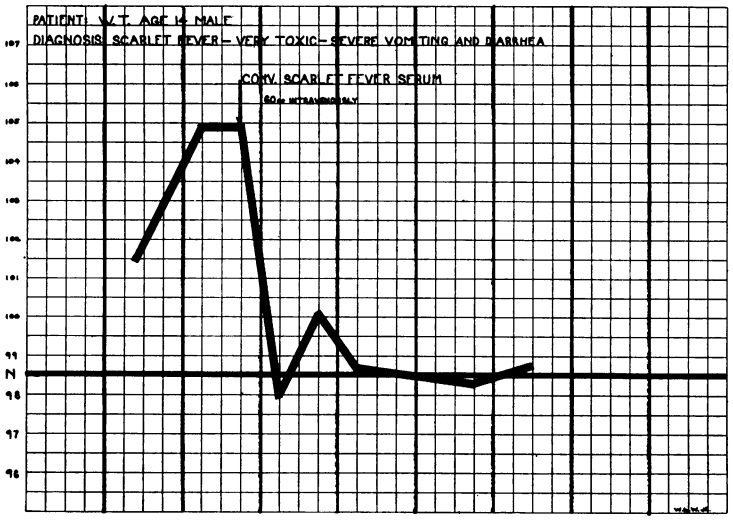


This serum has been named convalescent serum since it is prepared from the blood of individuals who are convalescing from or have recently recovered from infectious diseases. A better name is "convalescents' serum".

My interest in convalescent serums was aroused six or seven years ago for several reasons.

First: Several convalescent serums have been proved, by a large experience, in many places, to have marked efficacy in prophylaxis or therapy, or both.

Second: Convalescent serums, which, of course, are human serums, are safe agents to use and practically never cause reactions, even when administered intravenously. These properly prepared human serums have been demonstrated to be as nearly bland material for intravenous administration as anything known to me. Febrile reactions, chills or serum sickness are extremely unusual, occurring in not more than ½ to 1 per cent of the instances, and have never, to my knowledge, caused concern or alarm to the attending physician. Sensitization and anaphylaxis, in my experience, are unknown. All this is in contradistinction to the risks from the injection of animal serums, even though animal serums have been much improved in this regard in recent years. In our experience, there are no reactions at all following the intramuscular injection of the properly prepared human serums, with the possible exception of a very occasional, mild serum sickness from seven

to ten days later, which has never required medication.

Third: The field for investigation is extremely large, and needs intensive work.

The serum is prepared according to the rigid regulations of the U. S. Public Health Service, and the laboratory, having satisfied these requirements, has received a federal license. Only Wassermann negative serums, which have been proved bacteriologically sterile, are used. These are pooled, usually in lots of thirty individual serums. Preservative is added, followed by Berkefeld filtration and bottling. Sterility tests are repeated on the bottled serum, and each pool is held at least seven days before being released by a negative sterility test.

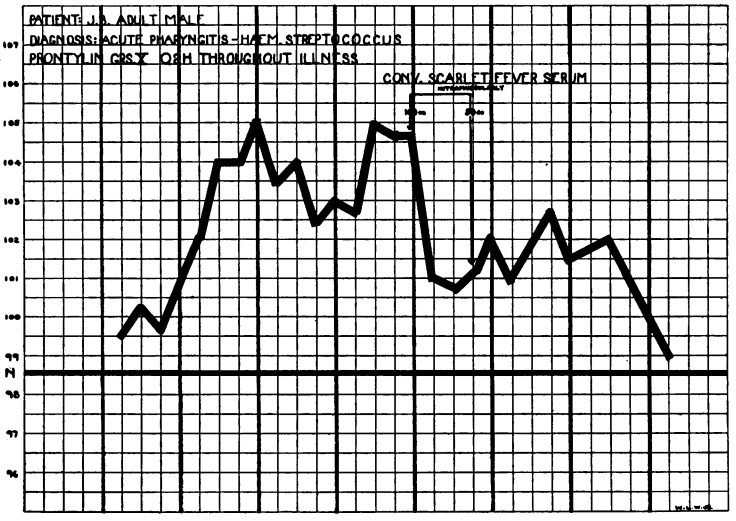
Extreme care and gentleness are used in handling the blood and serum, so as to prevent even a tinge of hemolysis, and bleedings are made only at least three hours after the donor's previous meal (so as to minimize the possibilitiy of food proteins being present in the serum).

It is my conviction that these precautions have eliminated reactions from the use of these human serums practically to the vanishing point. An experience of five years, covering thousands of injections of different types of convalescent serum administered by many physicians, both intravenously and intramuscularly, has demonstrated the practicability of preparing human serums which can be injected with no risk of severe reactions and with only the rare occurrence of a mild reaction.

Since all blood cells are removed by Berkefeld filtration, there is no possibility of agglutinable cells being present and causing a reaction. Also, whatever agglutinins the pooled serum contains, apparently are diluted sufficiently by the patient's entire circulating blood to prevent reactions. This also is the explanation of why blood transfused from universal donors into type II or III recipients has not caused reactions (except possibly in rare instances).

The serum has not caused sensitization, even when injections have been given to children at ten day intervals to prevent the reappearance of measles in a children's institution. With this procedure hospital wards can be kept open continuously even in the midst of epidemics.

Only adult donors are used, except in times of great prevalence of these two exanthemata (scarlet fever and measles), when children of fifteen or over may be used, after receiving the signed consent of the parents. Adults furnish 250 cc. of blood (by vein puncture) at each bleeding, for which they receive $5. This yields a net of about 100 cc.



of serum, after carrying out serological and sterility tests. The first bleeding can be made from recent convalescents after an afebrile period of seven days. Bleedings can be repeated in men at two week, and in women at three week intervals, without any deleterious effect and without any decrease in their hemoglobin percentage. Our data show that, on the contrary, the hemoglobin increases. It has been demonstrated that no significant fall in potency occurs in the serum secured from an individual for, at least, four months after onset in scarlet fever and measles. This period may be longer, and if investigation in progress demonstrates this, the source of supply will be correspondingly increased. Serum kept at four degrees centigrade retains its potency for at least a year.

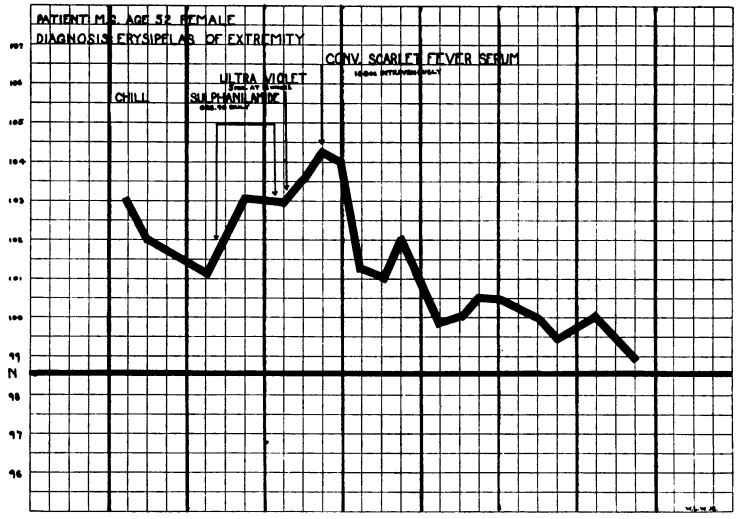
It might be well to discuss measles convalescent serum first.

Undoubtedly you will be interested to know that in 1916 Dr. William H. Park (with Zingher's cooperation) was the first in this country to employ convalescent serum for the prevention or attenuation of measles. This work was carried out independently, the same year as that of Nicolle and Conseil,[2] who published their results in 1918, Dr. Park not publishing until 1924.[3,4,5] Since these publications, more or less sporadic studies have been made in many places but only in recent years have centers been organized in a few European and American cities making enough convalescent serum available for extensive use. All of these trials, both small and large, have demonstrated the marked effi-

ciency of this method of measles prevention or attenuation.

Measles is usually considered a mild disease, inconvenient but inevitable. Therefore, it might be surprising to learn that in infants up to one year of age, who contract measles, the mortality rate is 8 per cent, in the one to two year age group 5 per cent and in those from two to three years old 1.5 per cent. These fatalities are caused mainly by the not uncommon serious complications of measles, such as pneumonia and mastoiditis. But from ten years of age on the mortality rate is much less, yet not insignificant, i.e., 0.1 per cent to 0.2 per cent. Stated in another way, 95 per cent of all deaths from measles occur in children four years old and under. Accordingly, the older a child is when accidentally infected with measles, the less likely he is to suffer serious complications or death. One further illustration, quoted from Godfrey,[6] is very illuminating. In New York State, from 1915-1924 there were 35,930 cases of measles reported among children under three years of age, in places of less than 200,000 population. Of these, 1,441 died, a fatality rate of 4 per cent. Had these attacks of measles been postponed until the children were between five and fourteen years old, only fifty-four would have died and the lives of 1,387 children in this group would have been saved. In other words, if there were a method which did no more than allow one to postpone measles until after children reached their fifth year, many lives could be saved. Apparently, it is not generally known that such a method does exist. If used within five days after exposure, it can prevent the disease in up to 95 per cent of those exposed, thereby postponing the contraction of measles till the children are older and in a more resistant age group when again accidentally exposed. The method has the further advantage, that if used within one week after exposure it can modify the infection to a mild, attenuated measles, practically sure to be free from serious complications. This attenuated measles is often so mild that it is difficult to diagnose, and yet the attenuated attack apparently confers sufficient permanent active immunity to prevent the disease occurring again.

It has been shown that the maximum percentage of prevention is achieved only if the serum is injected intramuscularly within five days after exposure. The minimum dose for children five years old or less is 5 cubic centimeters and for older children one cubic centimeter for every year of their age. Prevention can then be expected in from 70 per cent to 95 per cent of the injected children. Even in those instances



where complete prevention does not occur, a modified and attenuated attack will occur in all but 3 per cent to 5 per cent of the total group. One can readily see the advantage of limiting measles in healthy children to this mild disease with its subsequent immunity. As a matter of fact, attenuation should be the method of choice except in debilitated or sick children, in children five years of age or less, and in children exposed accidentally in hospitals and institutions. The reason for attempting complete protection in all children not over five years old, even though they are robust and in good health, is that the mortality from measles is confined mainly to this lower age group.

The full dose of serum has some chance of preventing the disease even if administered between the fifth and seventh day after exposure, and even if it fails to prevent the disease, usually causes attenuation. On and after the eighth day of exposure very little protection can be expected.

For attenuation, which is advised as the method of choice in healthy children over five years of age, one-half of the usual dose of serum should be injected not later than the fifth day of exposure, or the full dose from the sixth to the seventh day.

It also is well known that pooled normal adult serum is as efficient in the prophylaxis of measles as the specific convalescent serum, but it must be used in four times the amount, and normal whole blood in about eight times the quantity.[7,8] The disadvantage, formerly, in using normal

serum was the larger amount which had to be injected.

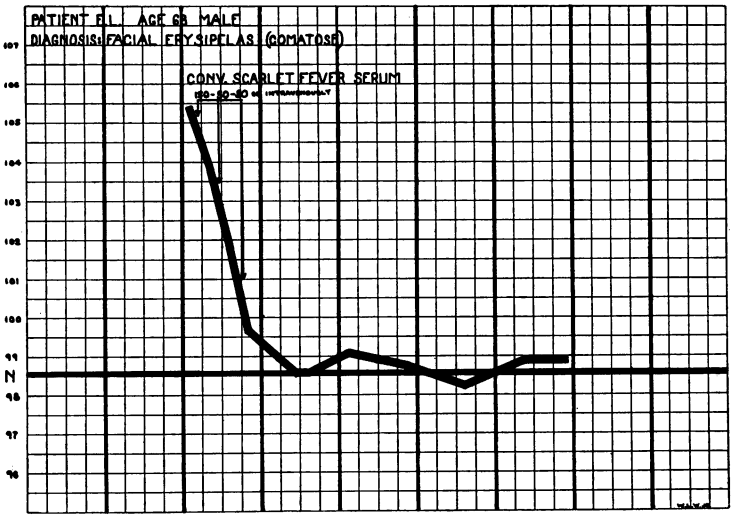
However, now we have several methods available for concentrating serum, and, thereby, reducing the amount of immune measles serum to be injected to the same volume needed when convalescent serum itself is injected. One method, which was developed recently in our laboratory, is by concentrating the serum in sterile, viscose casings; another is by precipitating the globulin of the serum, which was investigated by Dr. Samuel Karelitz[9,10,11] with the cooperation of Dr. K. G. Falk and Mr. C. Greenwald of the Research Laboratory of the Department of Health in the preparation of the globulin fraction. There, also, are several methods of freezing and drying serum, and redissolving it in a small amount of sterile distilled water.

There is no other method of preventing measles except with material obtained from human blood or similar sources (placental globulin,[12,13] with which I have had no experience).

In 1914, again it was Dr. Park who carried out the first work in this country with convalescent scarlet fever serum. This work was done under his direction by Zingher.[14,15]

Many reports since, in many countries, have shown the marked therapeutic value of pooled convalescent scarlet fever serum when this is given in large enough amounts and especially when administered intravenously early in the disease. The beneficial results have been so definite that in many articles recommendations are made for the organization of agencies for collecting and distributing convalescent serum. Blood, yielding potent serum, can be drawn on the twentieth day after the onset of illness, provided the patient is convalescing and has been fever free for at least seven days; and further bleedings may be made at two or three week intervals for a period of four months from the onset of the illness. About eight years ago, with the cooperation of the Chicago Department of Health and of a number of colleagues, and with a grant of funds, it was possible for me to organize the Samuel Deutsch Convalescent Serum Center at Michael Reese Hospital, and similarly, three years ago the Milwaukee Convalescent Serum Center at Columbia Hospital, Milwaukee. Some of the observations in Chicago have been published with Hoyne and Levinson.[16]

Eight hundred and seventy-two children, giving no previous history of scarlet fever, and unavoidably exposed in their homes to this disease, were passively immunized with from 10 to 20 cc. of pooled convalescent



serum, and only 2 per cent developed mild scarlet fever and 1 per cent genuine scarlet fever. In similarly exposed home contacts, Park states that in his experience about 10 per cent contract scarlet fever; and Gordon's findings in Detroit were 15 per cent. From 90 to 93 per cent were protected who were expected to contract the disease.

The doses for prophylaxis which we are recommending and which seem to be giving excellent results are 10 cc. by intramuscular injection to children up to five years of age, 15 cc. to those whose age is from five to ten years and 20 cc. for older children.

The results of therapy have been published of 947 severely ill hospitalized patients and 983 home treated patients of varying degrees of severity, 1,930 patients in all. The hospitalized patients were treated in the Chicago Municipal Contagious Disease Hospital under the direction of Dr. Hoyne.[16] Only severely sick patients received serum, usually on admission, and 6,282 mildly or moderately ill patients, admitted to the hospital during the same period, treated symptomatically and not receiving serum, served as controls.

Some of the findings can be briefly re-stated. Patients without septic complications showed an average fall of temperature of two and a half degrees in the first twenty-four hours and a total of three degrees in the first forty-eight hours when they received the convalescent serum within the first three days of their illness.

Not infrequently the disease was rapidly aborted, and even a toxic

patient with a temperature of 104-105 degrees was converted in twelve hours into a convalescent patient, with normal temperature, followed by an uninterrupted rapid convalescence.

When the serum was given from the fourth to sixth days of the disease the temperature drop was from one-half to one degree less. With the decline of temperature in the patients treated early, there was a corresponding and marked diminution of toxicity, fading or disappearance of the rash, relief from angina, nausea and vomiting, return of appetite, and shortening of the period of illness. Most patients with complications on admission or mildly ill but later developing complications were also greatly benefited by serum.

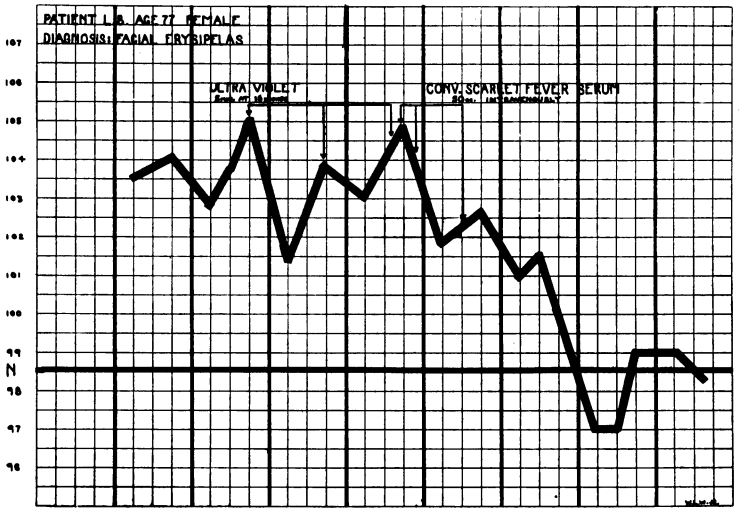
The evidence definitely shows also that severely ill, serum treated individuals developed a smaller number of less severe complications than the mildly or moderately ill in the control group not receiving serum.

The dosage, depending on the size of the individual and the severity of the illness, varied from 20 to 100 cc. It was administered intravenously and occasionally had to be repeated.

The value of intravenous administration over the intramuscular method cannot be over-emphasized. When the serum is injected into the vein it is distributed immediately throughout the entire blood stream and entire body. Hence, therapeutic action begins immediately. However, it takes from fourteen to sixteen hours for maximum absorption to occur after intramuscular administration, and even then the potency of the serum in the blood is only one-half of what it would have been had the same dose been given into the vein. It is the safety with which one can administer human serum that allows us to recommend the intravenous method rather than any other.

It is well recognized that a specific, therapeutic serum must be administered early in the course of an infectious disease, in order to secure maximum curative results. This holds just as true with the early administration of convalescent scarlet fever serum as with any other serum, such as diphtheria antitoxin. If one is to use convalescent scarlet fever serum therapeutically in severely ill scarlet fever patients, this serum should be administered in proper doses intravenously as soon as the diagnosis is made.

Another important use of convalescent scarlet fever serum is in the treatment of various types of hemolytic streptococcal infections



other than those arising from scarlet fever.[17] The reason for this, apparently, is that virulent, hemolytic streptococci causing various types of infection are closely related to those occurring in scarlet fever. They give rise to similar toxins which are neutralized by similar antitoxins.

Since the convalescent serum laboratory has been opened in New York, many physicians have used convalescent scarlet fever serum, on our advice, in the treatment of a large number of patients with severe streptococcal infections of the limbs, with streptococcal pneumonia, with severe forms of erysipelas, with streptococcal blood stream infections, and other serious types of streptococcal infections. All of these patients have been desperately ill, and the lives of many have been despaired of, even after all other types of treatment have been used. Many of these patients have made rapid recovery. Considering the desperate plight of these patients the physicians have considered many of these results to be quite startling. A statistical analysis of these results is impossible, because it is impossible to secure a control group of similar patients. Once a therapeutic agent is known to be of value it cannot be denied to anyone, and, therefore, the observation of a control, untreated group is impossible. One can estimate the significance of the results on the basis of previous experience.

Recently a very remarkable drug, sulphanilamide, has been extensively used in the treatment not only of streptococcal infections, for which it was introduced originally, but for other types of infection as

well. Many of the results with sulphanilamide treatment have been remarkable, but peculiarly enough it has been found by a number of observers to cause very little or no benefit in the treatment of scarlet fever.[18] It has been found, also, that sulphanilamide, at times, causes toxic effects and may even cause disaster; therefore, this potent drug must be used with care and at times must be discontinued. Some of the results referred to above in the treatment of patients desperately ill with various types of streptococcal infections have been achieved when sulphanilamide failed or when sulphanilamide had to be discontinued.

It should be emphasized again that convalescent serum is as nearly bland and innocuous a material as we know of, and, when properly prepared, in our experience has never produced any bad effects, which caused concern to the attending physicians. Whereas the exact method of action of sulphanilamide is not known, some experimental work by Rosenthal[19,20] indicates that a specific, therapeutic serum may complement the action of sulphanilamide, so that these two substances act synergistically. This means that when given together the beneficial effect is greater than the summation of the effect of each given separately. Therefore, during the past year since sulphanilamide has been available, some patients have received both of these agents simultaneously with excellent results.

It has been found that convalescent scarlet fever serum is an excellent material for producing the Schultz-Charlton blanching phenomenon, which, at times, is an important aid in the diagnosis of a scarlet fever rash. One cubic centimeter of this serum should be injected intracutaneously, and this small amount of serum, put up in ampoules, can be obtained at our laboratory. Again the use of human serum for this test avoids the use of animal serum with the possibility of reactions, sensitization, etc.

The Manhattan Convalescent Serum Laboratory is located in the Research Laboratory of the City Department of Health, on the same grounds where Dr. Park years ago did the first work in this field in this country. It is a non-profit organization, and its work has been made possible by the grant of funds from the Nathan Hofheimer, New York and Friedsam Foundations, and the Lederle Laboratories.

In order to maintain a supply of serum it is necessary to charge the cost of production of these serums. Until now the laboratory has not become self-supporting, but it is hoped that it will become so in the

future.

The demand for serum by physicians and hospitals has become so great that it is only with the greatest difficulty that we have been able to secure a sufficient supply to satisfy these demands. We need the help of all physicians in our endeavors to secure a sufficient amount of convalescent serum. Physicians can be of the greatest service in advising their private adult and adolescent patients immediately after recovery from measles or scarlet fever to cooperate with the Manhattan Convalescent Serum Laboratory. Only 250 cc. of blood are taken at a time, and for this each donor is paid $5 immediately. In our experience with many thousands of donors this has never caused the donor any harm. Since we take special care to make this a painless procedure with a small intracutaneous injection of novocain, the donors willingly return at three-week intervals for a period of four months to do their share in furnishing serum to aid others, especially children, exposed to or suffering from the disease from which the donors have just recovered. Physicians, also, have been extremely cooperative in advising their patients to help in this work.

The laboratory appreciates the help that has been given by many physicians, and will endeavor to maintain its effort to cooperate with physicians and hospitals in the control and treatment of infectious diseases.

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ANNOUNCEMENT OF EDWARD N. GIBBS MEMORIAL PRIZE

IT IS announced by The New York Academy of Medicine, 2 East 103 Street, New York City, that a sum of approximately $1,000 is available under the Edward N. Gibbs Memorial Prize toward original research in Diseases of the Kidney during 1938.

Candidates, who must be physicians who have been graduated at least three years and be residents of the United States, shall submit "evidence of research already performed and of facilities to prosecute research upon the causation, pathology and new methods of treatment of diseases of the kidney".

The award may be continued through not more than three years to any one individual.

Applications with the required evidence should be addressed to The New York Academy of Medicine prior to June 1st.